PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 256.3CIPWO	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/IB2004/000012	International filing date *(day/month/year)* 07.01.2004	Priority date *(day/month/year)* 11.04.2003
International Patent Classification (IPC) or national classification and IPC A61K31/403		
Applicant RANBAXY LABORATORIES LIMITED et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10.05.2004	01.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Gavriliu, D Telephone No. +49 89 2399-8274

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/000012

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-39 as originally filed

   Claims, Numbers

   1-28 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 4-7, 1, 8 and 18 (as regard the prodrugs and metabolites)

because:

☒ the said international application, or the said claims Nos. 4-7 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1, 4, 8 and 18(with respect to prodrugs and metabolites)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/000012

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-3,8-28
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-3,8-28
Industrial applicability (IA)	Yes:	Claims	1-3,8-28
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

For reasoning with regards to unsearched subject-matter, see Form PCT/ISA/210 of the International Search Report. No International Preliminary Examination will be carried out with respect to subject-matter which is not coverd by the search report (Rule 66.1(e)PCT)(Claims 1, 4, 8 and 18-with respect to prodrugs and metabolites).

Claims 4-7 relate to subject-matter considered by this Authority to be covered by the provision of Rule 67.1(iv)PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claims(article 34(4)(a)(i)PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. **Reference is made to the following documents:**

D1: WO 02/04402 A (BANYU PHARMA CO LTD ;MATSUDA KENJI (JP); KURIHARA HIDEKI (JP); OGI) 17 January 2002 (2002-01-17) & EP 1 302 458 A (BANYU PHARMACEUTICAL CO, LTD.) 16 April 2003 (2003-04-16)

D2: WO 02/053564 A (ALMIRALL PRODESFARMA AG ;BUIL ALBERO MARIA ANTONIA (ES); FERNANDEZ) 11 July 2002 (2002-07-11)

D3: CA-A-2 155 320 (FUJISAWA PHARMACEUTICAL CO) 19 August 1993 (1993-08-19)

D4: EP-A-0 863 141 (BANYU PHARMA CO LTD) 9 September 1998 (1998-09-09)

D5: US-B1-6 313 312 (GIBSON STEPHEN PAUL ET AL) 6 November 2001 (2001-11-06)

D6: US-A-5 164 402 (BRIGHTY KATHERINE E) 17 November 1992 (1992-11-17)

As D4 is an international patent application in Japanese and in order to avoid any misunderstanding, the family member document EP 1302458 is used to assess the novelty and inventive step of the present application.

2. **Novelty** (Article 33(1) and (2)PCT)

The present application discloses 2-hydroxyacetic derivative of formula (I)(see present Claim 1) as muscarinic receptor antagonists.
The present compounds differ from the D1-D4 compounds on the account of the 3-azabicyclo[3.1.0]-hexan ring, from the D5 compounds on the account of the monosubstitution in position 6 of the 3-azabicyclo[3.1.0]-hexan ring (present case-instead of bi-substitution in D5) and from the D6 compounds on the account of the N-substituent of the above-mentioned azabicyclo ring as well as on the account of the substituent on the carboxamide function from the 6 position of the same ring (see Claims 1 of the present case and of D6). Consequently, the novelty of the present subject-matters acknowledged.

3. **Inventive step** (Article 33(1) and (3)PCT)

The present application describes 2-hydroxyacetic acid derivatives as muscarinic receptor antagonists, useful to treat respiratory, urinary or gastrointestinal system disorders.

D1, which is regarded as being the closest prior art, discloses 2-aryl-2-hydroxy-acetates as muscarinic receptor antagonists, treating the same diseases as in the present case. The compounds disclosed by D1 differ from the present compounds only through the nature on the ring, which is linked on the ethanoate moiety (see e.g. compounds of formula (II) of Claims 22, 29 of D1 when k=1 and the present compounds when X=O).

The problem underlying the present invention can however not to be seen in providing further 2-hydroxyacetic derivative for the following reasons:

D2 discloses quinuclidine derivative as muscarine receptor antagonists (see compounds of formula I, when R6 is hydroxy group).

D3 discloses acetamide derivative which have anticholinergic activity, being useful for treating urinary or gastrointestinal system disorders (see page 1 of D3). The main difference between the present compounds and the examples 1-7, 10-12, 21, 25 of D3 consist in the replacement of the present azabicyclo ring with another heterocycle.

Since, the documents D1-D3 disclose compounds which have always the same R1R2CHOH-CO-Z moiety as in the present case and on the other hand there are different heterocycles which can be present, instead of the present azabicyclo ring, without loss of the activity (see e.g. the examples of D3, and the claims 22 and 27 of D1 where the above-mentioned group corresponding to the present azabicyclo ring can vary from pyrrolidine, piperidine, tetrahydropiperidine or even 8-azabicyclo[3.2.1]octane) it is considered that the skilled person would have expected that the desired activity will be maintained in such similar compounds (compounds for which it is changed only a heterocycle, which seems from the prior art documents not to be important for the maintenance of the activity).

The problem underlying the present application should thus be seen in providing novel 2-hydroxyacetic acid derivatives with unexpected or surprising effects compared to those of the closest prior art.

An inventive step cannot be recognized as it is not yet shown by appropriate information, e.g. in form of experimental data, that substantially all the claimed compounds have un unexpected property or improved activity over the structurally closest prior art compounds (D1), which is attributable to the distinguishing feature of the invention.

4. **Industrial applicability** (Article 33(4)PCT).

For the assessment of the present claims 4-7 on the question whether they are industrial applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may also allow, however, claims to a known compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*

WO2004/004629	15.01.2004	08.07.2002
WO2004/018422	04.032004	23.08.2002

These documents are related to 6-substituted 3-azabicyclo[3.1.0]hexane compounds as muscarinic receptors antagonists.